



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) **EP 1 240 134 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:

**23.02.2005 Bulletin 2005/08**

(21) Application number: **00962683.9**

(22) Date of filing: **15.12.2000**

(51) Int Cl.7: **C07C 245/16**

(86) International application number:  
**PCT/GB2000/003563**

(87) International publication number:  
**WO 2001/047869 (05.07.2001 Gazette 2001/27)**

(54) **PROCESS FOR THE PREPARATION OF DIAZOMETHANE**

VERFAHREN ZUR HERSTELLUNG VON DIAZOMETHAN

PROCEDE DE PREPARATION DE DIAZOMETHANE

(84) Designated Contracting States:  
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE TR**

(30) Priority: **23.12.1999 GB 9930454**

(43) Date of publication of application:  
**18.09.2002 Bulletin 2002/38**

(73) Proprietor: **Phoenix Chemicals Limited  
Bromborough, Merseyside CH62 3PW (GB)**

(72) Inventors:  
• **WARR, Antony, John  
Upton Chester CH2 1HX (GB)**  
• **PROCTOR, Lee  
Maeshasn Denbighshire DH7 4QX (GB)**

(74) Representative: **W.P. THOMPSON & CO.  
Coopers Building,  
Church Street  
Liverpool L1 3AB (GB)**

(56) References cited:  
**US-A- 5 459 243 US-A- 5 817 778  
US-A- 5 854 405**

- **CHEMICAL ABSTRACTS, vol. 110, no. 5, 30  
January 1989 (1989-01-30) Columbus, Ohio, US;  
abstract no. 38611c, YAMAGUCHI, MASATO:  
"Preparation of diazomethane ether solution"  
page 506; column 2; XP002154960 & JP 06  
351366 A (KURITA WATER INDUSTRIES, LTD) 4  
March 1988 (1988-03-04)**
- **CHEMICAL ABSTRACTS, vol. 91, no. 19, 5  
November 1979 (1979-11-05) Columbus, Ohio,  
US; abstract no. 157184q, RUEHLE, PAUL H ET  
AL: "A convenient large scale diazomethane  
generator" page 592; column 2; XP002154961 &  
CHEM. IND., no. 7, 1979, pages 255-6, London**

**EP 1 240 134 B1**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

## Description

**[0001]** Diazomethane ( $\text{CH}_2=\text{N}=\text{N}$ , also known as azimethylene or diazirine) is a highly reactive gas with a wide range of utility in chemical syntheses. It reacts rapidly with carboxylic acids to form the corresponding methyl esters, generally in high yield, with the evolution of gaseous nitrogen. In like manner diazomethane reacts with phenols, enols and alcohols to form methyl ethers with concomitant release of nitrogen; the rate of reaction depending on the acidity of the substrate. A further example of its use is the formation of carbon to carbon bonds with substrates such as acid chlorides and anhydrides. The so formed  $\alpha$ -diazoketones are themselves useful intermediates. Further examples are its use in cycloaddition reactions with olefins to form cyclopropanes and nitrogen heterocycles. Similarly chain extension or ring expansion of ketones and conversion of ketones to epoxides can be readily achieved with diazomethane. Still further examples of its use include formation of viral protease inhibitors. A number of viral protease inhibitors including those used to combat HIV are derived from three-carbon amino acid isosteres. An example of these viral protease inhibitors is Nelfinivir Mesylate (Agouron Laboratories). The crucial three-carbon fragment can be built from a two-carbon functionalised amino acid using diazomethane in a modified Arndt-Eistert reaction. This approach is particularly attractive since reaction with diazomethane does not compromise the chiral integrity of the amino acid.

**[0002]** Diazomethane is a powerful carcinogen, allergen and is highly poisonous. However the principle impediment to its use is that it is highly explosive. Whilst the toxic properties of diazomethane may be obviated by judicious plant design and good manufacturing practice, its sensitivity to explosion places greater restraints on its use.

**[0003]** The technical literature for the lab-scale synthesis of diazomethane cautions against the use of ground-glass joints and specifically designed firepolished glassware is recommended. The Aldrich Chemical Company, Inc., Milwaukee, Wisconsin, USA markets a "large-scale" DIAZALD<sup>®</sup> apparatus capable of generating a solution of up to 300 millimoles of diazomethane in diethyl ether by single batch reaction. See Black, T. H., "The Preparation and Reactions of Diazomethane", *Aldrichimica Acta* 16(1) 3-10 (1983).

**[0004]** A "large-scale" preparation is disclosed by Acevedo et al in United States Patent No. 5,459,243, "Apparatus and Processes for the Large Scale Generation and Transfer of Diazomethane", issued October 17, 1995. The reactions disclosed are performed on the 100 millimole scale and generate dilute solutions of diazomethane in dichloromethane.

**[0005]** A batch process for the production of gaseous diazomethane, "A New Method for the Preparation of Diazomethane" is disclosed by De Boer, T.H. J., and Backer, H. J. See *Recueil* 73 229-234 (1954). The process comprises introducing a solution of potassium hydroxide in a mixture of Carbitol - water to p-toly sulphonylmethylnitrosamide in anisole. A gentle flow of nitrogen is passed through the apparatus and the liberated gaseous diazomethane is obtained in 48% yield. The paper goes on to disclose that when the diazomethane was absorbed immediately in an excess of benzoic acid in ether, the yield was 63%.

**[0006]** More recently *Chemistry in Industry*, 21 February 1994, page 122/123, in a follow up letter to a publication in the same journal dated 5 November, 1990, cautions against the production of gaseous diazomethane because of the explosive risks. This is consistent with Bernd Eistert - "Synthesis with Diazomethane" which states "Gaseous diazomethane, even on dilution with nitrogen, likewise may undergo explosive decomposition, especially at temperatures of 100°C or higher".

**[0007]** Indeed it is because of the explosive nature of gaseous diazomethane that the skilled man has tended towards production and use of diazomethane in dilute solutions.

**[0008]** Aerojet - General Corporation ("Aerojet") is the only company to date to have published procedures to produce diazomethane on a truly large scale.

**[0009]** A large-scale batch production process for the production of solutions of diazomethane is disclosed by Aerojet in United States Patent No. 5,817,778, "Large Scale Batch Process for Diazomethane", issued October 6, 1998 and European Patent Publication No. EP 0 916 649 A1, "Large Scale Batch Process for Diazomethane", published May 19 1999. Preparations of diethyl ether solutions of diazomethane are disclosed on the 50 gram-mole to 25,000 gram-mole scale.

**[0010]** A continuous process for the production of solutions of diazomethane has been disclosed by Aerojet in United States patent No. 5,854,405, "Continuous Process for Diazomethane from an N-methyl-N-Nitrosamine and from Methylurea through N-Methyl-N-Nitroso Urea", issued December 24, 1998 and European Patent Publication No. EP 0 916 648 A1, "Continuous Process for Diazomethane", published May 19 1999. This procedure involves dissolving an N-methyl N-nitroso amine in a mixture of two organic solvents - one of which is at least partially water miscible and dissolves the N-methyl-N-nitrosoamine, and the other is one that is substantially less water-miscible than the first and forms a separate phase with water and dissolves diazomethane. A stream of this solution is combined with a stream of an aqueous inorganic base, the aqueous and organic phases are permitted to settle after a suitable residence time and the phases are separated, the diazomethane being recovered as an organic solution. It is stated that because all the stages of the process can be conducted in the liquid phase, the formation of diazomethane vapour is avoided and the risk of detonation is reduced or eliminated. However, the process isolates the diazomethane in a flammable organic solvent which provides a fire risk.

[0011] In view of the versatility of diazomethane and its associated hazards a safe and efficient large-scale continuous process providing good yields and preferably obviating the need for volatile and flammable solvents whilst maintaining a low overall inventory of diazomethane is desirable.

[0012] While the invention will be described in connection with certain preferred embodiments, it is not intended to limit the invention to the particular embodiments. On the contrary, it is intended to cover all alternatives, defined by the appended claims.

[0013] The applicant has experimentally determined that the lower explosive limit (LEL) of diazomethane is 3.9%. (The LEL is a limit defined in air). By "diluting" the diazomethane in an inert gas such as nitrogen the explosive limit is increased to an experimentally determined value of, in the case of nitrogen, 14.7% allowing the applicant to operate at higher concentrations of diazomethane safely.

[0014] According to the present invention there is provided a continuous method for the production of diazomethane comprising the steps of feeding:

a diazomethane precursor dissolved in a first solvent, and  
a base dissolved in a second solvent into a reactor vessel where they react to generate diazomethane, and removing the resulting diazomethane as a gas substantially free of solvent with the aid of a diluent gas.

[0015] In order to maintain a steady state operation the resultant waste steam is removed. The waste stream may comprise any unreacted reactants, by-products of the reaction, solvents and any residual diazomethane remaining in solution.

[0016] Preferably the diazomethane precursor and the base are co-fed into the reactor vessel in a continuous stream and the diazomethane gas and the resultant waste stream are removed from the reactor vessel in a continuous manner. Alternatively the diazomethane precursor and base may be fed into the reactor vessel as intermittent or pulsed streams and the diazomethane gas and the waste stream may be removed from the reactor vessel as intermittent or pulsed streams.

[0017] Preferably the diazomethane precursor is dissolved in a first solvent and the base is dissolved in a second solvent.

[0018] It is however possible for the base to be fed into the reactor vessel in a solid form and/or a liquid diazomethane precursor to be selected thereby obviating the need for one or more of the first and second solvents.

[0019] In yet another embodiment the first solvent and second solvent are one of the same solvent or a mixture of the first and second solvent.

[0020] Preferably the generation and removal of diazomethane gas is aided/effected by the use of a sparge diluent gas, which may be introduced above (top-surface) and/or below (sub-surface) the reaction mixture. A sub-surface sparge diluent gas aids the mixing of the reaction mixture and helps displace the diazomethane gas from the reaction mixture. A top-surface diluent sparge further assists to displace the diazomethane gas. Both the top-surface and bottom surface sparges act as diluents and are adjusted to achieve the desired operating conditions.

[0021] Preferably the flow rates of the sparge diluent gas are such that the concentration of diazomethane gas is maintained below the explosive for the diazomethane in said sparge diluent gas.

[0022] When the sparge diluent gas is nitrogen the concentration of diazomethane in nitrogen is preferably maintained at below 14.7%.

[0023] Preferably the diazomethane generated - and displaced by the diluent sparge gas - is continuously reacted with the intended substrate at a rate which minimises the inventory of diazomethane within the reaction system.

[0024] By controlling the temperature of the reaction and controlling the flow rates of one or more of:

the diazomethane precursor;  
the base;  
the sparge diluent gas; and  
the waste stream  
a steady-state operation can be achieved at a given set of reaction conditions.

By maintaining the relative concentration of the reactants at a steady state, high yields and high purity diazomethane can be obtained.

[0025] The optimum steady state conditions are primarily a function of the rate of addition of the reactants (and any respective solvents used to introduce them into the reactor vessel), their respective concentrations in the reactor vessel, the rate at which the diluent sparge gas is fed into the reactor vessel, the reaction temperature and the rate at which the waste stream and diazomethane gas are removed.

[0026] By monitoring the concentration of the resulting diazomethane gas, the process can thus be controlled to achieve the desired operating conditions, for example, by controlling one or more of the factors effecting steady state,

## EP 1 240 134 B1

to optimise production and maintain safe operability.

**[0027]** In most cases the ratio of the base to diazomethane precursor is maintained at from, for example, 1.0 to 1.5:1 molar equivalents.

**[0028]** More preferably the ratio of base to diazomethane precursor is maintained in excess at from 1.1 to 1.4:1 molar equivalent, and most preferably at 1.2:1 molar equivalents.

**[0029]** Preferably the diazomethane precursor is an N-methyl N nitroso compound or a precursor thereof.

**[0030]** The preferred N-methyl N nitroso compounds are selected from the group consisting of N-methyl-N-nitroso-p-toluenesulphonamide; N-methyl-N-nitroso urea; N-nitroso-β-methylaminoisobutyl methyl ketone; N,N'-dimethyl-N,N'-dinitrosoterephthalamide; N-[N'-methyl-N-nitroso(aminomethyl)]benzamide and 1-methyl-3-nitro-1-nitrosoguanidine.

**[0031]** The preferred diazomethane precursor is N-methyl-N-nitroso -p-toluenesulphonamide.

**[0032]** The first solvent is preferably selected to:

i) be non volatile, ie. have a low vapour pressure;

ii) have a high boiling point;

iii) be non-flammable; and

iv) be water soluble.

**[0033]** By non-volatile it is preferred that the vapour pressure is below 666.61 Pa (5mm) at 25 °C and most preferably below 133.32 Pa (1mm) at 20°C.

**[0034]** By high boiling point it is preferred that the boiling point is above 95 °C, most preferably above 150°C.

**[0035]** By non-flammable it is preferred that the flash point is above 55 °C as defined under the UK Chemicals (Hazard Information for Packaging & Supply) Regulations 1994.

**[0036]** The preferred first solvents are shown in the table below which additionally give their flashpoint, boiling point and vapour pressure.

TABLE

| SOLVENT                         | FLASH POINT (°C) | BOILING POINT (°C) | VAPOUR PRESSURE          |
|---------------------------------|------------------|--------------------|--------------------------|
| Di(ethylene glycol) ethyl ether | 96               | 202                | 10.66 Pa (0.08mm) (20°C) |
| N,N'Dimethylformamide           | 58               | 153                | 519.96 Pa (3.9mm) (25°C) |
| N,N' Dimethylacetamide          | 70               | 165                | 266.64 Pa (2mm) (25°C)   |
| Hexamethylphosphoramide         | 105              | 231 (740mm)        | 9.33 Pa (0.07mm) (25°C)  |
| Dimethyl sulphoxide             | 96               | 189                | 55.99 Pa (0.42mm) (20°C) |
| Tetramethylene sulphone         | 165              | 285                | 1.33 Pa (0.01mm) (20°C)  |

**[0037]** They may be used alone or as mixtures of one or more of these with or without a second solvent.

**[0038]** The most preferred first solvent is dimethyl sulphoxide.

**[0039]** The base may be an inorganic or organic base.

**[0040]** The preferred bases are inorganic bases, such as, for example, sodium, potassium and barium hydroxide. Most preferred is potassium hydroxide.

**[0041]** Organic bases which are suitable include, for example, sodium and potassium methoxide, sodium and potassium ethoxide, sodium isopropoxide, sodium cyclohexoxide and quaternary ammonium or quaternary phosphonium hydroxides or alkoxides such as tetra-n-butylammonium hydroxide, cetylpyridinium hydroxide, benzyltrimethylammonium ethoxide, tetraethylphosphonium hydroxide, and n-butyltriethylphosphonium phenoxide.

**[0042]** The second solvent is preferably a polar solvent, most preferably water or a mixture of polar solvents either with or without a first solvent.

**[0043]** In some cases the first and second solvent are one of the same solvent or a mixture of the first and second solvents.

**[0044]** The sparge diluent gas may be any suitable gas that displaces or effects removal of the resulting diazomethane from the reaction mixture. Examples include nitrogen, helium, argon, carbon dioxide and air. Inert gases are preferred, and the most preferred is nitrogen.

**[0045]** Preferably a reaction temperature is maintained at between 25 °C and 70°C, most preferably at 40°C.

**[0046]** Any residual diazomethane which remains in the reaction mixture and is not removed as a gas, is destroyed by passing the waste stream, into a quench tank containing an acid medium. Preferably the waste stream is a single

phase aqueous waste stream.

**[0047]** The pH of the acid medium is preferably between pH 4 and 6, most preferably pH 5.5. The preferred acid is acetic acid although any suitable inorganic or organic acid could be used.

**[0048]** The steady state is controlled by reference to the yield and purity of the resulting diazomethane gas and its concentration in the diluent gas.

**[0049]** The invention, and more particularly the selection of preferred features overcome a number of problems or disadvantages associated with the known large scale processes for producing diazomethane. Some of the problems and/or disadvantages associated with such processes are set out below:

- They generally employ flammable or highly flammable solvents;
- They employ highly volatile solvents;
- They require a relatively large inventory of diazomethane;
- The processes generally require condensation of the diazomethane/solvent vapour stream;
- The processes are bi-phasic and require efficient mixing and subsequent separation by distillation or phase separation; and
- The processes generate solutions of diazomethane, which may limit the flexibility of the downstream chemistry.

**[0050]** The batch process requires mechanical agitation with the incumbent risk of hot spots, leaking stirrer glands and also requires the use of a phase transfer catalyst to achieve improved yields.

**[0051]** The benefits of the method of the invention and more particularly the preferred features of the invention are set out below:

The diazomethane is generated quickly and continuously removed and reacted in downstream chemistry. The process therefore operates with a very low inventory of diazomethane, minimising the principal explosive hazard; and the diazomethane so generated is substantially free of solvents, moisture and other contaminants. No additional drying of the diazomethane gas stream is necessary. The yield and purity of the diazomethane generated is very high and being substantially free of solvents and contaminants, allows flexible use in downstream chemical reactions.

**[0052]** The preferred solvents used in the process are non-volatile, have low vapour pressures, high boiling points, are non-flammable, and are water soluble. Environmental concerns arising from the process are therefore minimised.

**[0053]** The solvents used are chosen to ensure high solubility of the diazomethane precursor whilst minimising the concentration of diazomethane in solution.

**[0054]** The reaction system is a homogenous/single-phase system. The generation of diazomethane is therefore extremely rapid without the need for any catalysts and the yield of diazomethane is in excess of 90%.

**[0055]** The diazomethane is generated in a reactor vessel of basic design. The reactor vessel is a dedicated unit which requires no mechanical agitation and has no moving parts.

**[0056]** Reactants may be continually co-fed into the reactor vessel. The addition rates can be accurately controlled allowing a steady state operation at the desired diazomethane concentration to be quickly achieved and maintained.

**[0057]** The diazomethane generated is continually "stripped" from the reactor using a top-surface and/or a subsurface diluent gas sparge. By controlling the rate of diluent sparge gas, the yield of diazomethane can be optimised

**[0058]** By continually monitoring the generation, concentration and use of diazomethane on a real-time basis good steady-state process control can be achieved.

**[0059]** The process is highly flexible and very applicable to scale-up. Waste streams are continually rendered free of diazomethane by the application of aqueous acid. Treated waste is a homogenous single-phase and all components are soluble.

**[0060]** The invention will now be described in more detail by way of example only with reference to the Fig which is a schematic diagram of a process of the invention and the method outlined below.

**[0061]** Referring to the schematic diagram a feed tank was charged with a 15% (w/w) solution of potassium hydroxide. A second feed tank was charged with a 22.1% (w/w) solution of N-methyl-N-nitroso -p-toluenesulphonamide in dimethyl sulphoxide. Both tanks were connected via pumps and/or pressure fed feed tanks to liquid mass flow meters. Full instrumentation control is provided for feeds, level/pressure, temperature and on-line analysis. The internal reactor surfaces are preferably polished to minimise rough surface issues. The reaction system has been specifically designed to promote laminar flow. The potassium hydroxide solution flow rate was set at 1.00Kg/hour corresponding to a molar flow of potassium hydroxide of 2.67mol/hour. The N-methyl N-nitroso -p-toluenesulphonamide solution flow rate was set at 2.15Kg/hour corresponding to a molar flow of N-methyl-N-nitroso -p-toluenesulphonamide of 2.22mol/hour. Nitrogen was fed sub-surface and top surface through two mass flow controllers. The subsurface flow was set at a rate

of 0.98L/minute and the top-surface flow was set at a rate of 6.7L/minute. Commencement of the diazomethane reaction caused the temperature of the reaction mixture to rise cooling was applied to maintain the reaction temperature at the desired set point of 40°C. The diazomethane/nitrogen stream was continually monitored to ensure the concentration of diazomethane in the gas phase remained constant and below the explosive limit. The flow-rates of top-surface and/or subsurface nitrogen, potassium hydroxide/water and N-methyl-N-nitroso -p-toluenesulphonamide / dimethyl sulphoxide are adjusted to maintain the concentration of diazomethane at 10%. Typically at least 96% of the diazomethane produced is removed in the gas phase.

**[0062]** The diazomethane generated was removed in the diluent gas sparge and continuously reacted in subsequent downstream chemistry to minimise the inventory of diazomethane in the reaction system. The reactor was continually drained in order to achieve a constant reactant mixture level and maintain a steady state operation. The waste stream which may contain residual levels of diazomethane was rapidly quenched into a tank containing 80% aqueous acetic acid. The pH of the tank was maintained at pH 5.5. Waste from the reactor, typically contains 4% residual diazomethane. This procedure allows 90g to 93g of diazomethane to be produced per hour. The maximum inventory of diazomethane at any instance is 0.11g.

**[0063]** The above reaction system is capable of producing 652Kg of diazomethane per year at 80% utilisation. By increasing the respective flow rates and adjusting the reactor volume, the system is capable of generating diazomethane at the rate of 5-10 kilos per hour (or 40 to 80 metric tonnes per year) whilst maintaining the inventory of diazomethane, in the reaction system at under 100g.

## Claims

1. A continuous method for the production of diazomethane comprising the steps of feeding:

a diazomethane precursor dissolved in a first solvent, and  
a base dissolved in a second solvent into a reactor vessel where they react to generate diazomethane, and removing the resulting diazomethane as a gas substantially free of solvent with the aid of a diluent gas.

2. A method as claimed in claim 1 which further comprises removing a waste stream.

3. A method as claimed in claim 1 or 2 wherein the diazomethane precursor and base are co-fed into the reactor vessel and the diazomethane gas and waste stream are removed from the reactor vessel in a continuous stream.

4. A method as claimed in claim 1 or 2 wherein the diazomethane precursor and/or base is/are fed into the reactor vessel and/or the diazomethane gas and/or the waste stream is/are removed from the reactor vessel in an intermittent or pulsed stream.

5. A method as claimed in any one of claims 1 to 4 wherein the first and second solvent are one and the same solvent or a mixture of the first and second solvents.

6. A method as claimed in any of the preceding claims wherein the diluent gas is a sparge diluent gas.

7. A method as claimed in claim 6 wherein the sparge diluent gas is introduced above the reaction mixture.

8. A method as claimed in claim 6 wherein the sparge diluent gas is introduced below the reaction mixture.

9. A method as claimed in claim 6 wherein the sparge diluent gas is introduced above and below the reaction mixture.

10. A method as claimed in any of claims 6 to 9 wherein the concentration of diazomethane gas is maintained at below the explosive limit for the diazomethane in said sparge diluent gas.

11. A method as claimed in claim 10 wherein when the sparge diluent gas is nitrogen, and the concentration of the diazomethane gas in nitrogen is maintained at below 14.7%.

12. A method as claimed in any of the preceding claims wherein a steady state is maintained by controlling the feed rate of one or more of:

the diazomethane precursor; and

the base; and/or the removal rate of one or more of the resulting diazomethane gas; and the waste stream and/or by controlling the temperature.

- 5 **13.** A method as claimed in any of the preceding claims wherein the base and diazomethane precursor are maintained at a ratio of from 1.0 to 1.5 : 1 molar equivalents of base : diazomethane precursor in the reactor vessel.
- 14.** A method as claimed in claim 13 wherein the ratio is maintained at 1.2 : 1 molar equivalents.
- 10 **15.** A method as claimed in any of the preceding claims wherein the diazomethane gas is substantially insoluble in the first and second solvent.
- 16.** A method as claimed in any of the preceding claims wherein the first solvent is selected from the group consisting of dimethyl sulphoxide;
- 15 di(ethylene glycol) ethyl ether;  
N,N'-dimethylformamide;  
N,N'-dimethyl acetamide;  
hexamethylphosphoramide ; and  
tetramethylenesulphone or mixtures of one or more of these with or without a second solvent.
- 20 **17.** A method as claimed in any of the preceding claims wherein the first solvent is or comprises a polar aprotic solvent.
- 18.** A method as claimed in any of the preceding claims wherein the first solvent is or comprises dimethyl sulphoxide.
- 25 **19.** A method as claimed in any of the preceding claims wherein the base is an inorganic base.
- 20.** A method as claimed in claim 19 wherein the inorganic base is selected from the group consisting of potassium hydroxide, sodium hydroxide and barium hydroxide.
- 30 **21.** A method as claimed in claim 19 or 20 wherein the inorganic base is potassium hydroxide.
- 22.** A method as claimed in any of claims 1 to 18 wherein the base is an organic base.
- 35 **23.** A method as claimed in claim 22 wherein the organic base is selected from the group consisting of sodium or potassium methoxide, sodium or potassium ethoxide, sodium isopropoxide, sodium cyclohexoxide and quaternary ammonium or quaternary phosphonium hydroxides or alkoxides.
- 40 **24.** A method as claimed in claim 23 wherein the quaternary ammonium or quaternary phosphonium hydroxides or alkoxides are selected from tetra-n-butylammonium hydroxide, cetylpyridinium hydroxide, benzyltrimethylammonium ethoxide, tetraethylphosphonium hydroxide and n-butyltri-ethylphosphonium phenoxide.
- 25.** A method as claimed in any of the preceding claims wherein the diazomethane precursor is a N-methyl N nitroso compound or a precursor thereof.
- 45 **26.** A method as claimed in any of the preceding claims wherein the diazomethane precursor comprises at least one compound selected from the group consisting of N-methyl-N-nitroso-p-toluenesulphonamide; N-methyl-N-nitroso urea; N-nitroso-β-methylaminoisobutyl methyl ketone; N,N'-dimethyl-N,N'-dinitrosoterephthalamide; N-[N'-methyl-N'-nitroso(aminomethyl)]benzamide and 1-methyl-3-nitro- 1-nitrosoguanidine.
- 50 **27.** A method as claimed in claim 26 wherein the diazomethane precursor is N-methyl-N-nitroso-p-toluenesulphonamide.
- 28.** A method as claimed in any of the preceding claims wherein the second solvent is a polar solvent or a mixture of a polar solvent with or without a first solvent.
- 55 **29.** A method as claimed in any of the preceding claims wherein the diluent gas comprises at least one gas selected from the group consisting of an inert gas, carbon dioxide and air.

## EP 1 240 134 B1

30. A method as claimed in claim 29 wherein the inert gas is nitrogen, helium or argon.
31. A method as claimed in claim 30 wherein the diluent gas is nitrogen.
- 5 32. A method as claimed in claim 12 wherein a steady state is maintained at a temperature of between 25 °C and 70°C.
33. A method as claimed in claim 32 where the temperature is maintained at 40°C.
- 10 34. A method as claimed in claim 2 wherein any residual diazomethane in the waste stream is fed into a quench tank containing an acid medium to destroy it.
35. A method as claimed in claim 34 wherein the quench tank is maintained at a pH of 4-6.
- 15 36. A method as claimed in claim 35 wherein the pH is maintained at pH 5.5.
37. A method as claimed in any of claims 34 to 36 wherein the acid is an inorganic acid or an aqueous solution of an organic acid.
- 20 38. A method as claimed in any of claims 34 to 37 wherein the acid is acetic acid.
39. A method as claimed in any of the preceding claims which method is conducted in a stainless steel reactor vessel comprising a base having a full bore bursting disk connected to a quench tank; a heat transfer surface connected to heating and/or cooling means; a thermoprobe; a waste outlet valve; addition ports; top-surface and bottom surface diluent gas sparge ports and a gas outlet port.
- 25 40. A method as claimed in any of the preceding claims wherein the diazomethane gas is used in a downstream reaction.
- 30 41. A method as claimed in any of claims 1 to 40 wherein the diazomethane gas is stored.

### Patentansprüche

- 35 1. Kontinuierliches Verfahren zur Herstellung von Diazomethan, umfassend die Schritte des Einspeisens:
- eines Diazomethan-Präkursors, der in einem ersten Lösungsmittel aufgelöst ist, und
- einer Base, die in einem zweiten Lösungsmittel in einem Reaktionsbehälter aufgelöst ist, worin sie zur Bildung von Diazomethan reagieren, und
- 40 Entfernen des resultierenden Diazomethans als ein Gas, das weitgehend frei von Lösungsmittel ist, mit Hilfe eines Verdünnungsgases.
- 45 2. Verfahren nach Anspruch 1, das weiter das Entfernen eines Abwasserstromes umfasst.
3. Verfahren nach Anspruch 1 oder 2, worin der Diazomethan-Präkursor und die Base zusammen in den Reaktionsbehälter gespeist und das Diazomethangas und der Abwasserstrom aus dem Reaktionsbehälter in einem kontinuierlichen Strom entfernt werden.
- 50 4. Verfahren nach Anspruch 1 oder 2, worin der Diazomethan-Präkursor und/oder die Base in den Reaktionsbehälter gespeist wird/werden und/oder das Diazomethangas und/oder der Abwasserstrom aus dem Reaktionsbehälter in einem intermittierenden oder gepulsten Strom entfernt wird/werden.
- 55 5. Verfahren nach einem der Ansprüche 1 bis 4, worin das erste und zweite Lösungsmittel ein und dasselbe Lösungsmittel sind oder ein Gemisch aus den ersten und zweiten Lösungsmitteln sind.
6. Verfahren nach einem der vorangehenden Ansprüche, worin das Verdünnungsgas ein Verdünnungsgas zum Durchblasen ist.

## EP 1 240 134 B1

7. Verfahren nach Anspruch 6, worin das Verdünnungsgas zum Durchblasen über dem Reaktionsgemisch eingeführt wird.
- 5 8. Verfahren nach Anspruch 6, worin das Verdünnungsgas zum Durchblasen unter dem Reaktionsgemisch eingeführt wird.
9. Verfahren nach Anspruch 6, worin das Verdünnungsgas zum Durchblasen über und unter dem Reaktionsgemisch eingeführt wird.
- 10 10. Verfahren nach einem der Ansprüche 6 bis 9, worin die Konzentration von Diazomethangas bei unter der Explosionsgrenze für das Diazomethan in genanntem Verdünnungsgas zum Durchblasen aufrechterhalten wird.
11. Verfahren nach Anspruch 10, worin, wenn das Verdünnungsgas zum Durchblasen Stickstoff ist und die Konzentration des Diazomethangases in Stickstoff bei unter 14,7 % aufrechterhalten wird.
- 15 12. Verfahren nach einem der vorangehenden Ansprüche, worin ein stationärer Zustand durch Kontrolle der Einspeisungsrate von einem oder mehr von:
- dem Diazomethan-Präkursor; und
- 20 der Base; und/oder der Entfernungsrate von einem oder mehr des resultierenden Diazomethangases; und dem Abwasserstrom und/oder durch Kontrolle der Temperatur aufrechterhalten wird.
13. Verfahren nach einem der vorangehenden Ansprüche, worin die Base und der Diazomethan-Präkursor bei einem Verhältnis von 1,0 bis 1,5 : 1 Moläquivalenten von Base : Diazomethan-Präkursor im Reaktionsbehälter aufrechterhalten werden.
- 25 14. Verfahren nach Anspruch 13, worin das Verhältnis bei 1,2 : 1 Moläquivalent aufrechterhalten wird.
- 30 15. Verfahren nach einem der vorangehenden Ansprüche, worin das Diazomethangas weitgehend im ersten und zweiten Lösungsmittel unlöslich ist.
16. Verfahren nach einem der vorangehenden Ansprüche, worin das erste Lösungsmittel aus der Gruppe ausgewählt ist, bestehend aus dem Dimethylsulfoxid;
- 35 Di(ethylenglycol)ethylether;  
N,N'-Dimethylformamid;  
N,N'-Dimethylacetamid;  
Hexamethylphosphoramid; und
- 40 Tetramethylsulfon oder Gemischen von einem oder mehreren von diesen mit oder ohne einem zweiten Lösungsmittel.
17. Verfahren nach einem der vorangehenden Ansprüche, worin das erste Lösungsmittel ein polares aprotisches Lösungsmittel darstellt oder umfasst.
- 45 18. Verfahren nach einem der vorangehenden Ansprüche, worin das erste Lösungsmittel Dimethylsulfoxid darstellt oder umfasst.
19. Verfahren nach einem der vorangehenden Ansprüche, worin die Base eine anorganische Base darstellt.
- 50 20. Verfahren nach Anspruch 19, worin die anorganische Base aus der Gruppe ausgewählt ist, bestehend aus Kaliumhydroxid, Natriumhydroxid und Bariumhydroxid.
21. Verfahren nach Anspruch 19 oder 20, worin die anorganische Base Kaliumhydroxid darstellt.
- 55 22. Verfahren nach einem der Ansprüche 1 bis 18, worin die Base eine organische Base darstellt.
23. Verfahren nach Anspruch 22, worin die organische Base aus der Gruppe ausgewählt ist, bestehend aus Natrium-

## EP 1 240 134 B1

oder Kaliummethoxid, Natrium- oder Kaliummethoxid, Natriumisopropoxid, Natriumcylcohexoxid und quartäre Ammoniumoder quartäre Phosphoniumhydroxide oder -alkoxide.

- 5
24. Verfahren nach Anspruch 23, worin die quartären Ammonium- oder quartären Phosphoniumhydroxide oder -alkoxide aus Tetra-n-butyl-ammoniumhydroxid, Cetylpyridiniumhydroxid, Benzyltrimethyl-ammoniummethoxid, Tetraethylphosphoniumhydroxid und n-Butyltriethyl-phosphonium-phenoxid ausgewählt sind.
- 10
25. Verfahren nach einem der vorangehenden Ansprüche, worin der Diazomethan-Präkursor eine N-Methyl-N-nitroso-Verbindung oder ein Präkursor davon darstellt.
- 15
26. Verfahren nach einem der vorangehenden Ansprüche, worin der Diazomethan-Präkursor mindestens eine Verbindung umfasst, die aus der Gruppe ausgewählt ist, bestehend aus N-Methyl-N-nitroso-p-toluensulfonamid; N-Methyl-N-nitrosoharnstoff; N-Nitroso-β-methylamino-isobutyl-methylketon; N,N'-Dimethyl-N.N'-dinitroso-terephthalamid; N-[N'-Methyl-N'-nitroso-(aminomethyl)]benzamid und 1-Methyl-3-nitro-1-nitrosoguanidin.
- 20
27. Verfahren nach Anspruch 26, worin der Diazomethan-Präkursor N-Methyl-N-nitroso-p-toluensulfonamid darstellt.
- 25
28. Verfahren nach einem der vorangehenden Ansprüche, worin das zweite Lösungsmittel ein polares Lösungsmittel oder ein Gemisch aus einem polaren Lösungsmittel mit einem ersten oder ohne ein erstes Lösungsmittel darstellt.
- 30
29. Verfahren nach einem der vorangehenden Ansprüche, worin das Verdünnungsgas mindestens ein Gas umfasst, das aus der Gruppe ausgewählt ist, bestehend aus einem inerten Gas, Kohlendioxid und Luft.
- 35
30. Verfahren nach Anspruch 29, worin das inerte Gas Stickstoff, Helium oder Argon darstellt.
- 40
31. Verfahren nach Anspruch 30, worin das Verdünnungsgas Stickstoff ist.
32. Verfahren nach Anspruch 12, worin ein stationärer Zustand bei einer Temperatur von zwischen 25 °C und 70 °C aufrechterhalten wird.
- 45
33. Verfahren nach Anspruch 32, worin die Temperatur bei 40 °C aufrechterhalten wird.
34. Verfahren nach Anspruch 2, worin jedwedes rückständiges Diazomethan im Abwasserstrom in einen Abkühlbehälter, enthaltend ein Säuremedium, gespeist wird, um es zu zerstören.
- 50
35. Verfahren nach Anspruch 34, worin der Abkühlbehälter bei einem pH von 4 - 6 aufrechterhalten wird.
36. Verfahren nach Anspruch 35, worin der pH bei pH 5,5 aufrechterhalten wird.
- 55
37. Verfahren nach einem der Ansprüche 34 bis 36, worin die Säure eine anorganische Säure oder eine wässrige Lösung einer organischen Säure darstellt.
38. Verfahren nach einem der Ansprüche 34 bis 37, worin die Säure Essigsäure darstellt.
39. Verfahren nach einem der vorangehenden Ansprüche, welches Verfahren in einem Edelstahlreaktionsbehälter durchgeführt wird, umfassend eine Basis mit einer Berstscheibe mit voller Bohrung, die an einen Abkühlbehälter angeschlossen ist; eine Wärmeübertragungsoberfläche, die an ein Heiz- und/oder Kühlmittel angeschlossen ist; eine Thermosonde; ein Abwasserablassventil; Zugabeöffnungen; Öffnungen zum Durchblasen des Verdünnungsgases an der Ober- und Unterseite und eine Gasauslassöffnung.
40. Verfahren nach einem der vorangehenden Ansprüche, worin das Diazomethangas in einer nachgeschalteten Reaktion verwendet wird.
41. Verfahren nach einem der Ansprüche 1 bis 40, worin das Diazomethangas gespeichert wird.

**Revendications**

1. Procédé continu de production de diazométhane comprenant les étapes consistant à introduire :
- 5 un précurseur de diazométhane dissout dans un premier solvant ; et  
une base dissoute dans un second solvant dans un récipient de réacteur dans lequel ils réagissent pour  
générer du diazométhane ; et  
à enlever le diazométhane sous la forme d'un gaz sensiblement dépourvu de solvant à l'aide d'un gaz diluant.
- 10 2. Procédé selon la revendication 1, comprenant en outre l'enlèvement d'un courant de déchets.
3. Procédé selon la revendication 1 ou 2, dans lequel le précurseur de diazométhane et la base sont co-introduits  
dans le récipient de réacteur et le gaz de diazométhane et le courant de déchets sont enlevés du récipient de  
réacteur en un courant continu.
- 15 4. Procédé selon la revendication 1 ou 2, dans lequel le précurseur de diazométhane et / ou la base est / sont introduit  
(s) dans le récipient de réacteur et / ou le gaz de diazométhane et / ou le courant de déchets est / sont enlevés  
du récipient de réacteur en un courant intermittent ou pulsé.
- 20 5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le premier et second solvants sont un seul  
et unique solvant ou un mélange du premier et du second solvants.
6. Procédé selon l'une quelconque des revendications précédentes, dans lequel le gaz diluant est un gaz diluant de  
rinçage.
- 25 7. Procédé selon la revendication 6, dans lequel le gaz diluant de rinçage est introduit au-dessus du mélange de  
réaction.
8. Procédé selon la revendication 6, dans lequel le gaz diluant de rinçage est introduit en dessous du mélange de  
réaction.
- 30 9. Procédé selon la revendication 6, dans lequel le gaz diluant de rinçage est introduit au-dessus et en dessous du  
mélange de réaction.
- 35 10. Procédé selon l'une quelconque des revendications 6 à 9, dans lequel la concentration du gaz de diazométhane  
est maintenue en dessous de la limite explosive pour le diazométhane dans ledit gaz diluant de rinçage.
11. Procédé selon la revendication 10 dans lequel quand le gaz diluant de rinçage est de l'azote, et la concentration  
du gaz de diazométhane dans l'azote est maintenue à moins de 14,7 %.
- 40 12. Procédé selon l'une quelconque des revendications précédentes, dans lequel un état stable est maintenu en con-  
trôlant le taux d'alimentation de l'un ou de plusieurs des éléments suivants :
- le précurseur de diazométhane ; et  
45 la base ; et / ou le taux d'enlèvement de l'un ou plus du gaz de diazométhane résultant ; et le courant de  
déchets et / ou en contrôlant la température.
13. Procédé selon l'une quelconque des revendications précédentes, dans lequel la base et le précurseur de diazo-  
méthane sont maintenus à un rapport allant de 1,0 à 1,5 / 1 équivalent molaire de base / précurseur de diazomé-  
thane dans le récipient de réacteur.
- 50 14. Procédé selon la revendication 13, dans lequel le rapport est maintenu à 1,2 / 1 équivalent molaire.
15. Procédé selon l'une quelconque des revendications précédentes, dans lequel le gaz de diazométhane est sensi-  
blement insoluble dans le premier et le second solvants.
- 55 16. Procédé selon l'une quelconque des revendications précédentes, dans lequel le premier solvant est sélectionné  
parmi le groupe constitué par le diméthylsulfoxyde ;

## EP 1 240 134 B1

l'éther de di(éthylène glycol) éthyle ;  
le formamide de N,N'-diméthyle ;  
l'acétamide de N,N'-diméthyle ;  
le phosphoramidate d'hexaméthyle ; et

le sulfone de tétraméthylène ou les mélanges de l'un ou de plusieurs de ceux-ci avec ou sans un second solvant.

17. Procédé selon l'une quelconque des revendications précédentes, dans lequel le premier solvant est ou comprend un solvant aprotique polaire.

18. Procédé selon l'une quelconque des revendications précédentes, dans lequel le premier solvant est ou comprend du diméthylsulfoxyde.

19. Procédé selon l'une quelconque des revendications précédentes, dans lequel la base est une base inorganique.

20. Procédé selon la revendication 19, dans lequel la base inorganique est sélectionnée parmi le groupe constitué par l'hydroxyde de potassium, l'hydroxyde de sodium et l'hydroxyde de baryum.

21. Procédé selon la revendication 19 ou 20, dans lequel la base inorganique est de l'hydroxyde de potassium.

22. Procédé selon l'une quelconque des revendications 1 à 18, dans lequel la base est une base organique.

23. Procédé selon la revendication 22, dans lequel la base organique est sélectionnée parmi le groupe constitué de méthoxyde de sodium ou de potassium, d'éthoxyde de sodium ou de potassium, d'isopropoxyde de sodium, de cyclohexoxyde de sodium et d'hydroxydes ou d'alkoxydes d'ammonium quaternaire ou de phosphonium quaternaire.

24. Procédé selon la revendication 23, dans lequel les hydroxydes ou alkoxydes d'ammonium quaternaire ou de phosphonium quaternaire sont sélectionnés parmi l'hydroxyde de tétra-n-butylammonium, l'hydroxyde de cétalpyridinium, l'éthoxyde de benzyltriméthylammonium, l'hydroxyde de tétraéthylphosphonium et le phénoxyde de n-butyltri-éthylphosphonium.

25. Procédé selon l'une quelconque des revendications précédentes, dans lequel le précurseur de diazométhane est un composé de N nitroso de N-méthyle ou un précurseur de celui-ci.

26. Procédé selon l'une quelconque des revendications précédentes, dans lequel le précurseur de diazométhane comprend au moins un composé sélectionné parmi le groupe constitué de N-méthyl-N-nitroso-p-toluènesulfonamide ; N-méthyl-N-nitroso urée ; N-nitroso-β-méthylaminoisobutyl méthyle cétone ; N,N'-diméthyl-N,N'-dinitrosotéréphtalamide ; N-[N'-méthyl-N'-nitroso(aminométhyl)]benzamide et 1-méthyl-3-nitro-1-nitrosoguanidine.

27. Procédé selon la revendication 26, dans lequel le précurseur de diazométhane est du sulfonamide de N-méthyl-N-nitroso-p-toluène.

28. Procédé selon l'une quelconque des revendications précédentes, dans lequel le second solvant est un solvant polaire ou un mélange d'un solvant polaire avec ou sans un premier solvant.

29. Procédé selon l'une quelconque des revendications précédentes, dans lequel le gaz diluant comprend au moins un gaz sélectionné parmi le groupe constitué d'un gaz inerte, de dioxyde de carbone et d'air.

30. Procédé selon la revendication 29, dans lequel le gaz inerte est de l'azote, de l'hélium ou de l'argon.

31. Procédé selon la revendication 30, dans lequel le gaz diluant est de l'azote.

32. Procédé selon la revendication 12, dans lequel un état stable est maintenu à une température entre 25 °C et 70 °C.

33. Procédé selon la revendication 32, dans lequel la température est maintenue à 40 °C.

## EP 1 240 134 B1

34. Procédé selon la revendication 2, dans lequel tout diazométhane résiduel dans le courant de déchets est introduit dans un bac de trempe contenant un milieu acide pour le détruire.

5

35. Procédé selon la revendication 34, dans lequel le bac de trempe est maintenu à un pH de 4 à 6.

36. Procédé selon la revendication 35 dans lequel le pH est maintenu à pH 5,5.

10

37. Procédé selon l'une quelconque des revendications 34 à 36, dans lequel l'acide est un acide inorganique ou une solution aqueuse d'un acide organique.

38. Procédé selon l'une quelconque des revendications 34 à 37, dans lequel l'acide est de l'acide acétique.

15

39. Procédé selon l'une quelconque des revendications précédentes, lequel procédé est effectué dans un récipient de réacteur en acier inoxydable comprenant une base ayant un disque de rupture de passage intégral connecté à un bac de trempe ; une surface de transfert thermique connectée à un dispositif de chauffage et / ou de refroidissement ; une sonde thermique ; une valve de sortie des déchets ; des voies d'ajout ; des voies de rinçage du gaz diluant pour la surface supérieure et pour la surface inférieure et une voie de sortie du gaz.

20

40. Procédé selon l'une quelconque des revendications précédentes, dans lequel le gaz de diazométhane est utilisé dans une réaction en aval.

41. Procédé selon l'une quelconque des revendications 1 à 40, dans lequel le gaz de diazométhane est stocké.

25

30

35

40

45

50

55

